

We claim:

1. An isolated, modified ADAMTS4 protein with improved stability compared to a naturally-occurring, full-length ADAMTS4 protein, said modified ADAMTS4 protein differing from the naturally-occurring, full-length ADAMTS4 protein by at least one amino acid.
- 5 2. The modified ADAMTS4 protein of claim 1, wherein the naturally-occurring, full-length ADAMTS4 protein comprises the amino acid sequence recited in SEQ ID NO:15.
3. The modified ADAMTS4 protein of claim 1, wherein a difference in amino acid sequences between the modified ADAMTS4 protein and the naturally-occurring, full-length ADAMTS4 protein is introduced by altering at least one amino acid in the naturally-occurring, full-length ADAMTS4 protein using a method selected from the group consisting of substituting, deleting, inserting, and chemically modifying amino acid residues.
- 10 4. The isolated, modified ADAMTS4 protein of claim 1, comprising a deletion of all or a portion of an ADAMTS4 spacer domain, wherein the modified ADAMTS4 protein has aggrecanase activity.
- 15 5. The isolated, modified ADAMTS4 protein of claim 1, wherein said protein does not have auto-catalytic activity.
6. The isolated, modified ADAMTS4 protein of claim 1, wherein said protein comprises a peptide tag.
7. The isolated, modified ADAMTS4 protein of claim 1, wherein said protein comprises a mutation in ADAMTS4 catalytic domain that abolishes the aggrecanase activity of said modified ADAMTS4 protein.
- 20 8. The isolated, modified ADAMTS4 protein of claim 7, further comprising a deletion of all or a portion of ADAMTS4 spacer domain.
9. An isolated, modified ADAMTS4 protein with improved stability compared to an ADAMTS4 protein having an amino acid sequence recited in SEQ ID NO:15, said modified ADAMTS4 protein comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:17, 19, 22, 24, 26, 27, 29, 31, 32, 40, and 46-53.
- 25 10. An isolated polynucleotide, said polynucleotide comprising a nucleotide sequence encoding the modified ADAMTS4 protein of claim 1.
- 30 11. An isolated polynucleotide, said polynucleotide comprising a nucleotide sequence encoding the modified ADAMTS4 protein of claim 9.

12. A vector comprising the polynucleotide of claim 10 in operative association with an expression control sequence.
13. A vector comprising the polynucleotide of claim 11 in operative association with an expression control sequence.
- 5 14. A method for producing a modified ADAMTS4 protein, said method comprising:
introducing a polynucleotide comprising a nucleotide sequence encoding the modified ADAMTS4 protein of claim 1 into a host cell;
incubating said host cell under conditions that allow expression of the modified ADAMTS4 protein from the polynucleotide; and
10 purifying the modified ADAMTS4 protein from the host cell.
15. A method for producing a modified ADAMTS4 protein, said method comprising:
introducing a polynucleotide comprising a nucleotide sequence encoding the modified ADAMTS4 protein of claim 9 into a host cell;
incubating said host cell under conditions that allow expression of the modified
15 ADAMTS4 protein from the polynucleotide; and
purifying the modified ADAMTS4 protein from the host cell.
16. A method of identifying an inhibitor of the modified ADAMTS4 protein of claim 1, said method comprising the steps of:
determining the aggrecanase activity of the modified ADAMTS4 protein;
20 contacting the modified ADAMTS4 protein with a candidate agent;
determining the aggrecanase activity of the modified ADAMTS4 protein in the presence of said candidate agent; and
determining whether said candidate agent affects the activity of the modified ADAMTS4 protein.
- 25 17. A pharmaceutical composition for treating an aggrecanase-related disease, comprising:
(a) an inhibitor of the modified ADAMTS4 protein of claim 1 or an antibody that binds specifically of the modified ADAMTS4 protein of claim 1; and
(b) a pharmaceutically acceptable carrier.
18. The pharmaceutical composition of claim 17, wherein the antibody inhibits the
30 aggrecanase activity of the modified ADAMTS4 protein.

19. A method for treating an aggrecanase-related disease in a mammal, said method comprising the step of:

introducing into the mammal an effective amount of the pharmaceutical composition of claim 17.

5 20. The method of claim 19, wherein the aggrecanase-related disease is osteoarthritis.